13. (Amended) The method of claim 11, wherein the gene is a foreign gene.

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14. (Amended) The method of claim 13, wherein the foreign gene is a retroviral gene or a viral gene.

15. (2x Amended) The method of claim 11, wherein the gene is associated with a cancer, a central nervous system disorder, a metabolic disorder, a cardiovascular disorder, an autoimmune disorder, an infectious disease or an inflammatory disorder.

REMARKS

Claims 1-26, 29 and 34-47 are pending in the subject application. Claims 15-17, 19-23, 34-41 and 47 have been withdrawn from further consideration. Applicant has canceled claim 29 without prejudice and amended claims 1-3, 6, and 12-15 to introduce certain formatting changes. Applicant maintains that the amendments to the claims do not introduce an issue of new matter. Accordingly, claims 1-14, 18, 24-26 and 42-46 will be pending and under examination in the subject application upon entry of this Amendment.

Applicant annexes hereto as Exhibit A a marked-up version of the amended claims to show the changes made relative to the previous version thereof.

Applicant respectfully requests that, in view of the remarks made herein, the Examiner withdraw the outstanding rejections.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1-14, 18, 24-26, 29 and 42 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response to the rejection to claims 1-14, 18, 24-26, 29 and 42-46, based on the Examiner's assertion that the phrase "binds sufficiently close" renders the claims indefinite, applicant traverses the rejection, noting that the amended claims do not recite the term objected to by the Examiner.

In response to the rejection of claims 2, 3, 12, 13 and 14, based on the Examiner's assertion that there is insufficient antecedent basis for the term "the target gene", applicant traverses the rejection, noting that the claims as amended do not recite the term objected to by the Examiner.

In response to the rejection of claim 9, based on the Examiner's assertion that it is unclear from the specification which elements are required for "a pLS vector" rendering the claim indefinite, applicant traverses. The Examiner has acknowledged that the specification contains a diagram of a pLS vector. Applicant maintains that one skilled in the art would know the features required for a pLS vector from the diagram contained in the specification.

In response to the rejection of claim 18, based on the Examiner's assertion that there is insufficient antecedent basis for the term "infectious disease", applicant traverses and notes that amended claim 15 provides sufficient antecedent basis for the term "infectious disease" in claim 18.

In response to the rejection of claim 29, applicant respectfully points out that claim 29 has been canceled without prejudice, rendering the rejection thereof moot.

In view of the above remarks, applicant maintains that claims 1-14, 18, 24-26 and 42 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1-14, 18, 24-26, 29 and 42-46 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

In response to the rejection of claim 29, applicant respectfully points out that this claim has been canceled without prejudice rendering the rejection thereof moot.

In response to the Examiner's rejection of claims 1-14, 18, 24-26 and 42-46, applicant respectfully traverses.

Briefly, claims 1-6 provide a chimeric protein for inhibiting the expression of a gene comprising a DNA methyltransferase whose DNA-binding activity is attenuated relative to that of naturally occurring DNA methyltransferase and a DNA binding protein linked thereto that binds to the gene's promoter sequence under conditions permitting the methylation of a methylation site within the promoter of the gene, thus inhibiting expression of the gene. Claims 11-14, 18, 24-26 and 29 provide a method for

inhibiting expression of a gene which comprises contacting of the gene with a chimeric protein for inhibiting the expression of a gene comprising a DNA methyltransferase whose DNA-binding activity is attenuated relative to that of naturally occurring DNA methyltransferase and a DNA binding protein linked thereto, so as to methylate the promoter, thus inhibiting expression of the gene. Claims 7-10 provide an expression vector encoding a chimeric protein for inhibiting the expression of a gene comprising a DNA methyltransferase whose DNA-binding activity is attenuated relative to that of naturally occurring DNA methyltransferase and a DNA binding protein linked thereto. Claims 42 and 43 provide a host cell comprising an expression vector encoding a chimeric protein for inhibiting the expression of a gene comprising a DNA methyltransferase whose DNA-binding activity is attenuated relative to that of naturally occurring DNA methyltransferase and a DNA binding protein linked thereto. Claims 44-46 provide a pharmaceutical composition comprising a therapeutically effective amount of an expression vector encoding a chimeric protein for inhibiting the expression of a gene comprising a DNA methyltransferase whose DNA-binding activity is attenuated relative to that of naturally occurring DNA methyltransferase and a DNA binding protein linked thereto and a pharmaceutically acceptable carrier.

The claimed invention is based on applicant's surprising discovery that a chimeric protein comprising a DNA methyltransferase whose DNA-binding activity is attenuated relative to that of naturally occurring DNA methyltransferase and a DNA binding protein linked thereto can methylate a methylation site within the promoter of a gene and thus inhibit expression of the gene.

In support of the rejection, the Examiner asserts that the

specification does not fully describe the genus of claimed chimeric proteins. In essence, the Examiner asserts that the specification does not disclose the structure of the species of the claimed genus of chimeric proteins in that it fails to describe any representative species by any identifying characteristics or properties other than function. In addition the Examiner cites UC California v. Eli Lilly in further support of the written description rejection.

In response, applicant maintains that the specification provides written description for the subject matter claimed. First, it is unnecessary that applicant set forth all possible chimeric proteins for establishing written description, or enablement for that matter. Rather, all that need be provided is a representative number of such chimeric proteins. Applicant maintains that a representative number of examples and their specific design and selection have been set forth in the specification. Specifically the Examiner has acknowledged that "[t]he specification provides guidance in the form of ... 2 working examples of the claimed chimeric protein - a mutant S.SssI linked via a 9 amino acid linker to a mutant LexA binding protein (see Example 3) for use in inhibiting expression from an HIV 5'-LTR (Examples 5 and 7) and Hepatitis B virus (Example 6)." These examples are found at, *inter alia*, page 44, line 24 to page 47, line 12, and page 52, line 34 to page 54, line 13. In addition, at, *inter alia*, pages 39-57 of the specification, applicant has described in sufficient detail methods for the design, selection and affinity maturation of other chimeric proteins.

Applicant further notes that, contrary to the Examiner's position, no structure/function relationship need be established for the claimed invention to be adequately described. Indeed, it

is sufficient for written description that (i) applicant has provided working examples of the chimeric proteins and (ii) that applicant has described how to design and select chimeric proteins without undue experimentation. In addition, applicant maintains that the text of UC California v. Eli Lilly quoted by the Examiner is inapplicable in this case, as it relates to "claims to genetic material" unique to a given species or class, and not to chimeric proteins such as those claimed here.

Accordingly, applicant maintains that the subject matter of the rejected claims is adequately described in the specification.

The Examiner also rejected claims 1-14, 18, 24-26, 29 and 42-46 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the rejection of claim 29, applicant respectfully points out that claim 29 has been canceled without prejudice rendering the rejection thereof moot.

In response to the Examiner's rejection of claims 1-14, 18, 24-26 and 42-46, applicants respectfully traverse. Applicant's traversal is based, where applicable, on the reasons set forth in response to the Examiner's written description rejection, and on the following reasons.

The test for enablement is whether one skilled in the art could, at the time of the invention, make and use the claimed invention based on the disclosure and information known in the art without undue experimentation. Applicant maintains that the claimed

invention satisfies the test for enablement, and that the Examiner has not set forth sufficient grounds for concluding otherwise.

In support of the rejection, the Examiner asserts that it would require undue experimentation to make and use the claimed invention. Specifically the Examiner asserts that in view of the factors detailed in In re Wands, (i.e., the quantity of the experimentation necessary, amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art and the relative skill of those in the art), undue experimentation would be necessary to practice the invention.

Applicant respectfully disagrees with the Examiner's position. First, and contrary to the Examiner's position, applicant notes that the breadth of the claims 1-6 is relatively narrow. That is, these claims provide only chimeric proteins comprising (i) a DNA methyltransferase whose DNA-binding activity is attenuated relative to naturally occurring DNA methyltransferase (as opposed to "any DNA methyltransferase ..." as stated by the Examiner) and(ii) a DNA binding protein linked thereto that binds to the gene's promoter sequence under conditions permitting the methylation of a methylation site in the promoter sequence of the gene (as opposed any "DNA binding protein ... that binds to a gene's promoter sequence") to permit methylation of a methylation site within the promoter. For the same reasons, the breadth of claims 11-14, 18, 24-26 and 44-46 is also relatively narrow.

Second, applicant maintains that the specification provides adequate guidance for practicing the claimed invention. That is, the experiments in the specification at, *inter alia*, page 44, line 24 to page 47, line 12, and page 52, line 34 to page 54,

line 13, showing working examples of the chimeric proteins, combined with a detailed description of methods for designing and selecting other protein chimera, would enable one to practice the invention as claimed without undue experimentation. Thus, appropriate guidance is provided by the specification.

Third, contrary to the Examiner's position, the ability to isolate proteins or nucleic acids encoding proteins with altered functionality is not highly unpredictable. The Examiner's positions appear to be based on his assertion that applicant has not provided a list of specific amino acid modifications and detailed description of the ways the protein structure relates to its function. The Examiner also asserts that it is not routine in the art to screen for modifications having the desired functionality.

Applicant submits that, contrary to the Examiner's position, applicant has fully described in the specification how to obtain the chimeric proteins as encompassed by the claims. In addition, applicant's description of methods for the design, selection and screening of other chimeras is sufficient for the purposes of enablement. The Examiner's assertion that the specification corroborates this alleged unpredictability is incorrect. The statement cited by the Examiner in support of this assertion does not relate to an alleged unpredictability in generating mutants, but relates to using random mutagenesis. Also, applicant's statement in the specification that it may be necessary to perform more that one iteration of the mutagenesis/selection process does not provide corroboration for the alleged unpredictability, but is merely a statement as to the quantity of routine experimentation that may be required. The fact that a larger quantity of experimentation may be required to practice the invention does not mean that it is not enabled, as long as

such experimentation is not undue.

Fourth, regarding the Examiner's rejection of claims 44-46, it appears to applicant that the Examiner objects to the intended use of the claimed pharmaceutical composition. The Examiner's belief that such pharmaceutical composition would not be effective in treating a disease has not been adequately supported. That is, the Examiner has not shown evidence that would support a position of lack of enablement for these claims.

Finally, with regard to the Examiner's rejection of claim 9, applicant notes, as the Examiner has acknowledged, that the specification contains a diagram of a pLS vector. In addition, the making of DNA vectors is routine in the art. Applicant maintains that one skilled in the art would know how to make and use a pLS vector from the diagram contained in the specification in view of what is known in the art, without undue experimentation. Applicant therefore maintains that the rejected claims are enabled.

In view of the above remarks, applicant respectfully maintains that claims 1-14, 18, 24-26 and 42-46 satisfy the requirements of 35 U.S.C. §112, first paragraph.

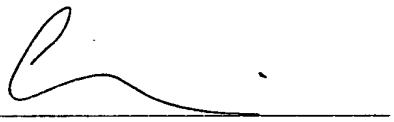
Conclusion

Applicant maintains that the pending claims are in condition for allowance, and thus, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $55.00 extension fee, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Assistant Commissioner for Patents
Washington, D.C. 20231.

3/5/03

Alan J. Morrison
Reg. No. 37,399

Date

Marked-up Version of the Amended Claims to Show Changes

1. (3X Amended) A chimeric protein for inhibiting the expression of a gene which comprises (1) a DNA methyltransferase whose DNA-binding activity is attenuated relative to that of naturally occurring DNA methyltransferase, and (2) a DNA binding protein linked thereto that binds [sufficiently close] to the gene's promoter sequence [to permit] under conditions permitting the methylation of a methylation site within the promoter, thus inhibiting expression of the gene.

2. (Amended) The protein of claim 1, wherein the promoter sequence of the [target] gene is a 5' long terminal repeat sequence of a human immunodeficiency virus-1 proviral DNA.

3. (Amended) The protein of claim 1, wherein the [target] gene comprises a retroviral gene, an adenoviral gene, a foamy viral gene, a parvoviral gene, a foreign gene expressed in a cell, an over expressed gene, or a misexpressed gene.

6. (3X Amended) The chimeric protein of claim 1, wherein the DNA methyltransferase is a *Spiroplasma* MQ1 DNA methyltransferase (*M.SssI* DNA methyltransferase) whose DNA-binding activity is attenuated relative to that of naturally occurring *M.SssI* DNA methyltransferase, or a mutated mammalian DNA methyltransferase whose DNA binding activity is attenuated relative to that of naturally occurring mammalian DNA methyltransferase.

12. (2x Amended) The method of claim 11, wherein the [target] gene is an endogenous gene.

13. (Amended) The method of claim 11, wherein the [target] gene is a foreign gene.